REMARKS

In the Claims

Claim 1 is amended to correct proper antecedent basis of the term "electrochemically determined information" to dependent claims 20-24 and 43-45.

Claim 2 has been amended to recite proper dependency upon claim 1 as amended.

Support for the amendments to claims 1 and 2 is to be found in claims 20-24 and 43-45 and in the specification at page 3, line 34 and continued on page 4, lines 1-3; at page 5, lines 11-15; and in Examples 1 and 8.

Claim 109 is amended to correct proper antecedent basis of the term "electrochemically determined information" to dependent claims 119-123.

Claim 112 has been amended to recite proper dependency upon claim 109 as amended.

Support for the amendments to claims 109 and 112 is to be found in claims 119-123, and in the specification at page 3, line 34 and continued on page 4, lines 1-3; at page 5, lines 11-15; and in Examples 1 and 8.

No new matter has been added by these amendments.

Applicants respectfully request entry of the present amendment.

Prior Rejections

1) Applicants thank the Examiner for withdrawing the rejections of claims 1-9, 11-25, and 91-105 under 35 USC § 112, second paragraph, and for withdrawing the rejections of claims 1-3, 11-18, 20-25, 91, 92, and 99-101 under 35 USC § 102(b).

Claim Rejections under 35 USC § 103(a)

2) The Examiner has rejected claims 1-18, 20-25, 43-45, 91-101, 109-116, and 119-129 under 35 USC § 103(a) as being unpatentable over Calzone et al. (Methods in Enzymology (1987) vol. 152, pp. 611-632) in view of Clinical Micro Sensors, Inc. (CMS; WO01/06016, published January 25, 2001).

> "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *Graham v. John Deere Co.*, 148 USPQ 459, 467 (S.Ct. 1966).
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> "In determining obviousness, "[i]t is not pertinent whether the prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure." By way of contrast, in determining novelty, a showing that the "prior art reference cited as anticipating a claimed invention. . .lack[ed] the characteristics of the claimed invention. . .would in fact negate the assertion that the claimed invention was described in the prior art." In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990).

3) Applicants have amended claim 1 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively degrading either hybridized, partially hybridized or unhybridized oligonucleotide probe, the degrading resulting in degraded oligonucleotide probe; and electrochemically determining information relating to the electrochemically active marker, wherein the electrochemically determined information relating to the electrochemically active marker correlates with the presence of the nucleic acid and wherein the electrochemically determined information relating to the electrochemically active marker correlates with the size and characteristics of the degraded or non-degraded oligonucleotide probe, the method resulting in probing for the nucleic acid".

Applicants have amended claim 109 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may

be present in the nucleic acid solution; selectively digesting hybridized oligonucleotide probe using a duplex specific exonuclease; and electrochemically determining information relating to the electrochemically active marker, wherein the electrochemically determined information relating to the electrochemically active marker correlates with the presence of the nucleic acid and wherein the electrochemically determined information relating to the electrochemically active marker correlates with the extent of digestion of the oligonucleotide probe, the method resulting in probing for the nucleic acid".

Applicants respectfully submit that neither Calzone nor CMS teach a method comprising determining information relating to the electrochemically active marker wherein the electrochemically determined information relating to the electrochemically active marker correlates with the size and characteristics of the degraded or non-degraded oligonucleotide probe.

Applicants submit that one of skill in the art would not have combined the teachings of Calzone et al. and CMS to improve the method of Calzone et al. and which would then have enabled the skilled artisan to determine electrochemically determined information relating to the electrochemically active marker that correlates with the size and characteristics of a degraded or non-degraded oligonucleotide probe. Applicants submit that it is not clear in the record that the teachings of Calzone et al. could be used with the electrochemically active markers as taught by CMS.

Applicants draw the Examiner's attention to the Specification at page 5, lines 11-15, where Applicants state: "(t)he present invention is based upon the observation that an electrochemically active marker such as metallocene exhibits different electrochemical characteristics depending upon whether or not it is attached to a nucleotide, whether or not that nucleotide is incorporated into an oligonucleotide or not, and the length of any such oligonucleotide". Applicants submit that this property would not have been predicted by one of skill in the art and was unexpected.

Applicants respectfully note that Calzone et al. teaches the use of radiolabeled nucleic acid probes for mapping gene transcripts by nuclease protection assays. Applicants note that

Calzone et al. teaches that the probes are prepared using DNA polymerase I, dNTPs, radiolabeled ATP to synthesize a complementary strand of a gene sequence of interest in M13 cloning vector. Calzone et al. do not teach using an oligonucleotide probe. Calzone et al. do not teach using an electrochemically active marker. Calzone et al. do not teach using an oligonucleotide probe labeled with an electrochemically active marker. Calzone et al. do not teach electrochemically determined information.

Calzone et al. teach probes copied from genomic inserts of 500 nucleotides (Calzone et al. at page 617, line 20); a probe of 540 nucleotides (ibid., at page 625, footnote, first line and on Fig. 2b); a probe fragment of length 75 nucleotides (ibid., at page 625, lines 2-3 and on Fig. 2a); probes that span at least one exon (ibid., Fig. 1); probes that can approach "the length of the M13 vector sequence in size" (ibid., page 618, line 5-7; M13 is typically between 6.4 and 7.2 kb in size); probes of approximately 100 nucleotides in size (ibid., page 619, second paragraph, last sentence); and a probe of approximately 2,480 nucleotides in size (ibid., Fig 3c and legend; 2060 + 420 = 2480 nucleotides).

Calzone et al. teach that "(s)ingle-stranded probes are frequently contaminated with a small amount of complementary-strand DNA which may protect the full length probe sequence from nuclease attack. Therefore the length of the probe sequences in RNA-DNA hybrids must be detectable shorter that that of the untreated probe" (ibid.. page 613, last paragraph and continues on page 614, lines 1-2).

Calzone et al. further address a problem caused by degraded template-probe hybrids that interferes with the detection of RNA-DNA hybrids. They warn that "all possible precautions should be taken to avoid degradation of the M13 template during probe synthesis and gel purification" (ibid., at page 618, lines 13-17).

Calzone et al. also consider probe degradation over time during storage teaching that "with time the probe becomes increasingly fragmented, reducing the fraction of probe molecules that form a discrete band in high-resolution acrylamide gels (ibid., at page 619, lines 14-16).

Applicants therefore submit that Calzone et al. do not teach oligonucleotide probes but also teach away from using an oligonucleotide probe (*viz.* degraded template-probe hybrids, fragmented probe).

Applicants respectfully submit that Clinical Micro Sensors, Inc. (CMS) do not teach "the electrochemically determined information relating to the electrochemically active marker correlates with the size and characteristics of the degraded or non-degraded oligonucleotide probe".

Applicants submit that CMS teaches detecting the presence or absence of cleaved probe and do not teach correlating the electrochemically determined information relating to the electrochemically active marker with the size or characteristics of degraded or non-degraded oligonucleotide probe. Applicants submit that this property would not have been predicted by one of skill in the art at the time the invention was made.

Applicants submit that CMS teaches that the "uncleaved primary probes are removed" and therefore a non-degraded probe cannot contribute to the CMS method of detecting the probe sequence (CMS at page 12, lines 13-14). Applicants further submit that CMS does not teach nor suggest a motivation to modify or to combine the teachings of CMS with those of Calzone et al. and which would have enabled the skilled artisan to determine electrochemically determined information relating to the electrochemically active marker that correlates with the size and characteristics of a degraded or non-degraded oligonucleotide probe.

Applicants submit that the record contains no evidence that a skilled artisan would have considered modification of the methods of Calzone et al. by use of the ETM labels and nucleases and methods of detecting ETM labels taught by CMS.

Applicants submit that the prior art and the claims at issue are different, the Calzone et al. reference lacks the characteristics of the claimed invention, and therefore that claim 1 is not unpatentable over Calzone et al. in view of Clinical Micro Sensors, Inc. Applicants

further submit that dependent claims 2-18, 20-25, 43-45, and 91-101 are therefore also not unpatentable over Calzone et al. in view of Clinical Micro Sensors, Inc.

Applicants submit that the prior art and the claims at issue are different and therefore that claim 109 is not unpatentable over Calzone et al. in view of Clinical Micro Sensors, Inc. Applicants further submit that dependent claims 110-116, and 119-129 are therefore also not unpatentable over Calzone et al. in view of Clinical Micro Sensors, Inc.

Applicants therefore respectfully request that the Examiner withdraw the rejections of claims 1-18, 20-25, 43-45, 91-101, 109-116, and 119-129 under 35 USC § 103(a).

4) The Examiner has rejected claim 93 under 35 USC § 103(a) as being unpatentable over Calzone et al. (Methods in Enzymology (1987) vol. 152, pp. 611-632) and Clinical Micro Sensors, Inc. (WO01/06016, published January 25, 2001) as applied to claims 1-18, 20-25, 43-45, 91-101, 109-116, and 119-129, and further in view of Nikiforov et al. (US Patent 5,518,900, issued May 21, 1996).

> "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *Graham v. John Deere Co.*, 148 USPQ 459, 467 (S.Ct. 1966).

> "In determining obviousness, "[i]t is not pertinent whether the prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure." By way of contrast, in determining novelty, a showing that the "prior art reference cited as anticipating a claimed invention. . .lack[ed] the characteristics of the claimed invention. . .would in fact negate the assertion that the claimed invention was described in the prior art." In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990).

5) Applicants have amended claim 1 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may

be present in the nucleic acid solution; selectively degrading either hybridized, partially hybridized or unhybridized oligonucleotide probe, the degrading resulting in degraded oligonucleotide probe; and electrochemically determining information relating to the electrochemically active marker, wherein the electrochemically determined information relating to the electrochemically active marker correlates with the presence of the nucleic acid and wherein the electrochemically determined information relating to the electrochemically active marker correlates with the size and characteristics of the degraded or non-degraded oligonucleotide probe, the method resulting in probing for the nucleic acid".

Applicants respectfully submit that, as recited above, Calzone et al. and CMS do not teach a method comprising determining information relating to the electrochemically active marker wherein the electrochemically determined information relating to the electrochemically active marker correlates with the size and characteristics of the degraded or non-degraded oligonucleotide probe.

Applicants submit that the prior art and the claims at issue are different, the Calzone et al. reference lacks the characteristics of the claimed invention, and therefore that claim 93, being dependent upon claim 1, is not unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. in view of Nikiforov et al.

Applicants therefore respectfully request that the Examiner withdraw the rejections of claim 93 under 35 USC § 103(a).

6) The Examiner has rejected claims 102-105 and 130-133 under 35 USC § 103(a) as being unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. (WO01/06016, published January 25, 2001) as applied to claims 1-18, 20-25, 43-45, 91-101, 109-116, and 119-129, in view of Heller et al. (US Patent 5,605,622, issued February 25, 1997).

> "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *Graham v. John Deere Co.*, 148 USPQ 459, 467 (S.Ct. 1966).

> "In determining obviousness, "[i]t is not pertinent whether the prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure." By way of contrast, in determining novelty, a showing that the "prior art reference cited as anticipating a claimed invention. . .lack[ed] the characteristics of the claimed invention. . .would in fact negate the assertion that the claimed invention was described in the prior art." In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990).

7) Applicants have amended claim 1 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively degrading either hybridized, partially hybridized or unhybridized oligonucleotide probe, the degrading resulting in degraded oligonucleotide probe; and electrochemically determining information relating to the electrochemically active marker, wherein the electrochemically determined information relating to the electrochemically active marker correlates with the presence of the nucleic acid and wherein the electrochemically determined information relating to the electrochemically active marker correlates with the size and characteristics of the degraded or non-degraded oligonucleotide probe, the method resulting in probing for the nucleic acid".

Applicants have amended claim 109 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively digesting hybridized oligonucleotide probe using a duplex specific exonuclease; and electrochemically determining information relating to the electrochemically active marker, wherein the electrochemically determined information relating to the electrochemically active marker correlates with the presence of the nucleic acid and wherein the electrochemically determined information relating to the electrochemically active marker correlates with the extent of digestion of the oligonucleotide probe, the method resulting in probing for the nucleic acid".

Applicants respectfully submit that, as recited above, Calzone et al. and CMS do not teach a method comprising determining information relating to the electrochemically active marker wherein the electrochemically determined information relating to the electrochemically active marker correlates with the size and characteristics of the degraded or non-degraded oligonucleotide probe.

Applicants have considered the "Heller et al." reference cited by the Examiner (US Patent 5,605,622) and respectfully point out that US Patent 5,605,622 as cited in the previous Office action (Notice of References Cited) is in fact a patent to Ferraro et al. and appears to be drawn to an unrelated art. Applicants are therefore unable to find or study the Heller reference.

Nevertheless, Applicants submit that the prior art and the claims at issue are different, the Calzone et al. reference lacks the characteristics of the claimed invention, and therefore that claims 102-105 and claims 130-133, being dependent upon claim 1 and claim 109 respectively, are not unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. in view of Heller et al.

Applicants therefore respectfully request that the Examiner withdraw the rejections of claims 102-105 and 130-133 under 35 USC § 103(a).

8) The Examiner has rejected claims 19, 117, and 118 under 35 USC § 103(a) as being unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. (WO01/06016, published January 25, 2001) as applied to claims 1-18, 20-25, 43-45, 91-101, 109-116, and 119-129, in view of Hall et al. (US Patent 5,994,069, issued November 30, 1999).

> "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *Graham v. John Deere Co.*, 148 USPQ 459, 467 (S.Ct. 1966).

> "In determining obviousness, "[i]t is not pertinent whether the prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure." By way of contrast, in determining novelty, a showing that the "prior art reference cited as anticipating a claimed invention. . .lack[ed] the characteristics of the claimed invention. . .would in fact negate the assertion that the claimed invention was described in the prior art." In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990).

9) Applicants have amended claim 1 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively degrading either hybridized, partially hybridized or unhybridized oligonucleotide probe, the degrading resulting in degraded oligonucleotide probe; and electrochemically determining information relating to the electrochemically active marker, wherein the electrochemically determined information relating to the electrochemically active marker correlates with the presence of the nucleic acid and wherein the electrochemically determined information relating to the electrochemically active marker correlates with the size and characteristics of the degraded or non-degraded oligonucleotide probe, the method resulting in probing for the nucleic acid".

Applicants have amended claim 109 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively digesting hybridized oligonucleotide probe using a duplex specific exonuclease; and electrochemically determining information relating to the electrochemically active marker, wherein the electrochemically determined information relating to the electrochemically active marker correlates with the presence of the nucleic acid and wherein the electrochemically determined information relating to the electrochemically active marker correlates with the extent of digestion of the oligonucleotide probe, the method resulting in probing for the nucleic acid".

Applicants respectfully submit that, as recited above, Calzone et al. and CMS do not teach a method comprising determining information relating to the electrochemically active

marker wherein the size and characteristics of the degraded or non-degraded oligonucleotide probe.

Applicants submit that the prior art and the claims at issue are different, the Calzone et al. reference lacks the characteristics of the claimed invention, and therefore that claim 19, and claims 117 and 118, being dependent upon claims 1 and 109 respectively, are not unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. in view of Hall et al.

Applicants therefore respectfully request that the Examiner withdraw the rejections of claims 19, 117, and 118 under 35 USC § 103(a).

CONCLUSION

With these arguments, Applicants believe that the application is in condition for allowance. If the US Patent Office believes that communication would further the prosecution of this application, then the appropriate US Patent Office personnel are invited to contact the Applicants' below-signed representative at their earliest convenience.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Bell & Associates Deposit Account No. 50-3194.

Dated and signed:

27th February 2009

Matthew Kaser, D.Phil.
Reg. No. 44,817

Bell & Associates,
58 West Portal Avenue, # 121,
San Francisco, California 94127
Tel: (510) 537-2040
Fax: (415) 276-6040
mkaser@bell-iplaw.com